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**THE EFFECT OF DIAZEPAM ON TOLERANCE
OF A MUCOUS MEMBRANE IRRITANT**

by

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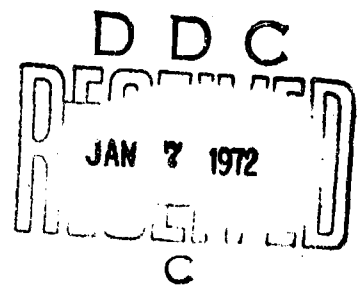
M. A. McColloch, 1LT

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THE EFFECT OF DIAZEPAM ON TOLERANCE
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Clinical Medical Sciences Department

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Task 1W062116AD2103

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FOREWORD

The work described in this report was authorized under Task 1W062116AD2103, Medical Effects of Chemical Agents, Clinical Evaluation of Chemical Agents. The experimental work was started in September and completed in December 1970.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25.

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DIGEST

Twenty-seven subjects selected on the basis of their MMPI (Minnesota Multiphasic Personality Inventory) scale scores were exposed to CS (o-chlorobenzylidene malononitrile), a potent mucous membrane irritant. Following initial exposure, the subjects were exposed to CS after intravenous injection of either 10 mg of diazepam or saline. Comparison of initial exposure times to times after injection indicated that exposure times for subjects were significantly increased by diazepam, particularly for subjects with elevated MMPI scale scores. These same subjects had slightly lower initial exposure times than subjects who did not have elevated MMPI scale scores. It is suggested that diazepam improves tolerance times by reducing anxiety and is therefore more effective in subjects with higher levels of anxiety.

THE EFFECT OF DIAZEPAM ON TOLERANCE OF A MUCOUS MEMBRANE IRRITANT

I. INTRODUCTION.

Diazepam is widely used as a minor tranquilizer, anticonvulsant, and muscle relaxant. Studies have shown that it reduces anxiety as measured by increased skin resistance and lower muscle tension during electric shock,¹ by decreasing autonomic nervous system response to stressful motion pictures,² and by decreasing scores on anxiety test batteries.³

However, the ability of diazepam to reduce anxiety seems to depend on the personality of the subject to whom the drug is given. In Barrett and DiMascio's study,³ normal male subjects who scored high on the anxiety test battery prior to receiving the drug showed a significant reduction in anxiety scores after 1 week of 6 mg three times daily of diazepam orally. Subjects who had low initial scores had a slight but non-significant increase in anxiety test scores under the same conditions. Frostad et al.¹ found significant differences in anxiety reduction following 60 mg of diazepam orally over a 3-day period, depending on normal male subjects' anxiety test scores and whether they were found to be action or nonaction oriented by psychological testing. In contrast, McDonald⁴ found no difference in anxiety scores of normal female volunteers grouped on the basis of anxiety test scores and action or nonaction orientation after a single oral dose of 5 or 10 mg of diazepam.

In the present study, the ability of nonpatient male volunteer subjects to tolerate exposure to CS (o-chlorobenzylidene malonitrile), a compound with potent mucous membrane irritant properties,⁵ before and

¹ Frostad, A. L., Forrest, G. L., and Bakker, C. B. Influence of Personality Type on Drug Response. *Amer. J. Psychiat.* 122, 1153-1158 (1966).

² Clemens, T. L., and Selesnick, S. T. Psychological Method for Evaluating Medication by Repeated Exposure to a Stressor Film. *Dis. Nerv. Syst.* 28, 98-103 (1967).

³ Barrett, J. E., and DiMascio, M. A. Comparative Effects on Anxiety of the "Minor Tranquilizers" in "High" and "Low" Anxious Student Volunteers. *Ibid.* 27, 483-486 (1966).

⁴ McDonald, R. L. The Effects of Personality Type on Drug Response. *Arch. Gen. Psychiat.* 17, 680-686 (1967).

⁵ Punte, C. L., Owens, E. J., and Guttentag, P. J. Exposures to Ortho-Chlorobenzylidene Malononitrile. *Arch. Environ. Health* 6, 366-374 (1963).

after intravenous injection of 10 mg of diazepam was investigated. Since it has been shown^{6, 7} that experimental efforts to allay anxiety resulted in lower estimates of the intensity of painful stimuli, it was predicted that the anxiety-reducing properties of diazepam would increase exposure times to CS. Subjects whose MMPI (Minnesota Multiphasic Personality Inventory) scale scores indicated greater anxiety were expected to have shorter initial exposure times but were expected to show greater improvement in tolerance to CS after injection of diazepam.

II. METHOD.

Twenty-seven US Army enlisted male volunteers were selected for this study on the basis of MMPI scores. In addition, all subjects received a physical examination, chest X-ray, and laboratory tests to exclude the presence of physical disease. All subjects had been previously exposed to CS no more than five times as a part of routine training. (Punte et al.⁵ have shown that tolerance times to CS do not increase with this number of exposures.)

Thirteen subjects whose MMPI scale scores (T scores with K correction) contained at least two clinical scale scores (with the exception of *Mf*) above 70 or one scale score above 80 were labeled as "abnormal" subjects. Fourteen subjects whose clinical scale scores with the exception of *Mf* were all below 70 were labeled as "normals." Each group was further divided into those who would receive saline and those who would receive diazepam.

Subjects were briefed concerning the experimental procedure on the day prior to exposure. They were shown the individual exposure chamber, which consisted of a wind tunnel into which the subject's head could readily be inserted or removed. Subjects were asked to remain in the chamber as long as they could, but no other attempt was made to motivate them. On the first experimental day, no injections were given and the subjects entered the chamber at 30-minute intervals. On the succeeding day, 13 men were given saline intravenously and 14 men were given 10 mg of diazepam intravenously 30 minutes prior to exposure. A rigorous attempt was made to avoid suggesting that the drug would have a positive or negative effect on CS exposure times. Each man was prevented from

⁶ Hill, H., Kornetsky, C., Flanary, H., and Wikler, A. Effects of Anxiety and Morphine on the Discrimination of Intensities of Painful Stimuli. *J. Clin. Invest.* 31, 473-480 (1952).

⁷ Kornetsky, C. Effects of Anxiety and Morphine on the Anticipation and Perception of Painful Radiant and Thermal Stimuli. *J. Comp. Physiol. Psychol.* 47, 130-132 (1954).

observing the reaction of other subjects. Experimenters assisting subjects in the exposure chamber had no advance knowledge of whether or not the subjects had received saline or diazepam.

CS was dissolved in 10% methylene dichloride to deliver a concentration of 2.5 mg/cu m in aerosol form. This concentration was verified following every fifth exposure.

III. RESULTS.

Table I shows the mean of subjects' MMPI scores on the three validity scales, the 10 clinical scales, and the A (anxiety) scale. Significant differences between "abnormal" and "normal" subjects are indicated.

Table I. MMPI Scale Scores of "Normal" and "Abnormal" Subjects

Scale	"Normals" (n = 14) means	"Abnormals" (n = 13) means	t
L (lie)	51.5	50.4	0.4
F (unusual responses)	51.4	66.5	3.8**
K (validity)	57.3	53.8	0.9
Hs (hypochondriasis)	50.6	60.9	2.6*
D (depression)	50.5	64.9	3.4**
Hy (conversion hysteria)	54.0	60.0	1.5
Pd (psychopathic deviant)	52.6	60.6	3.6**
Mf (masculine-feminine)	54.2	59.2	1.3
Pa (paranoia)	51.7	64.6	3.3**
Pt (psychasthenia)	51.5	69.5	5.6**
Sc (schizophrenia)	52.4	79.5	5.2**
Ma (mania)	58.3	72.9	4.3**
Si (social introversion)	45.0	51.9	2.1*
A (anxiety)	41.7	55.2	3.7**

*Significant beyond the 0.05 level.

**Significant beyond the 0.01 level.

The tolerance of a subject for CS was measured by the length of time he remained in the exposure chamber. In table II, the mean exposure times for all subjects for both the undrugged and drugged conditions are recorded. The mean exposure times for "normal" and "abnormal" subjects are also given.

Table II. Initial Exposure Times and Average Change in Exposure Time Following Diazepam and Saline

Group	Mean initial time	Mean differences in exposure times	
		After saline	After diazepam
	sec	sec	
All subjects	15 \pm 9	-1	+7*
"Normals"	17 \pm 10	-3	+3
"Abnormals"	13 \pm 8	+2	+10*

*P < 0.05 (difference between initial exposure time and times after diazepam by t test).

The mean of the initial times for the abnormal subjects was less than that of the normal subjects, but this result was not statistically significant. Injection of diazepam resulted in a significant improvement in tolerance times when difference scores for the total group under drugged and undrugged conditions were compared by t test. "Abnormal subjects" given diazepam showed a significant increase in exposure times using this method of analysis, but "normal" subjects did not. All subjects receiving diazepam showed significantly more improvement than subjects receiving saline when the differences between their initial exposure times and those after injection were compared ($t = 2.76$, $P < 0.05$).

IV. DISCUSSION.

Inspection of table I reveals that the "abnormal" group of subjects did have deviant MMPI scale scores and had significantly higher scores on 10 of the 14 scales investigated. The highest mean values for this group occurred on the Pt (psychasthenia), Sc (schizophrenia), and Ma (mania) scales, indicating a greater resemblance to psychiatric patients than the "normal" group of subjects. The assumption that this group had more anxiety than the normal group depends on the interpretation of elevated Pt and A scale scores. These scales correlate with the Taylor Manifest Anxiety Scale and the IPAT Anxiety Battery.⁸

⁸ Miller, N. B., Fisher, W. P., and Ladd, C. E. Psychometric and Rated Anxiety. Psychol. Rept. 20, 707-710 (1967).

That anxiety may be related to ability to tolerate exposure to CS is suggested by the lower mean exposure times of the "abnormal" group compared with those of the "normal" group, although this difference was not statistically significant. This might have been due to the relatively high concentration of CS which precluded large individual differences (mean initial exposure times for all subjects was only 15 seconds, with a standard deviation of 9 seconds). The improved tolerance to CS for the "abnormal" group after receiving a known anxiety-reducing agent does suggest that anxiety reduction played an important role in improving the tolerance of this group.

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